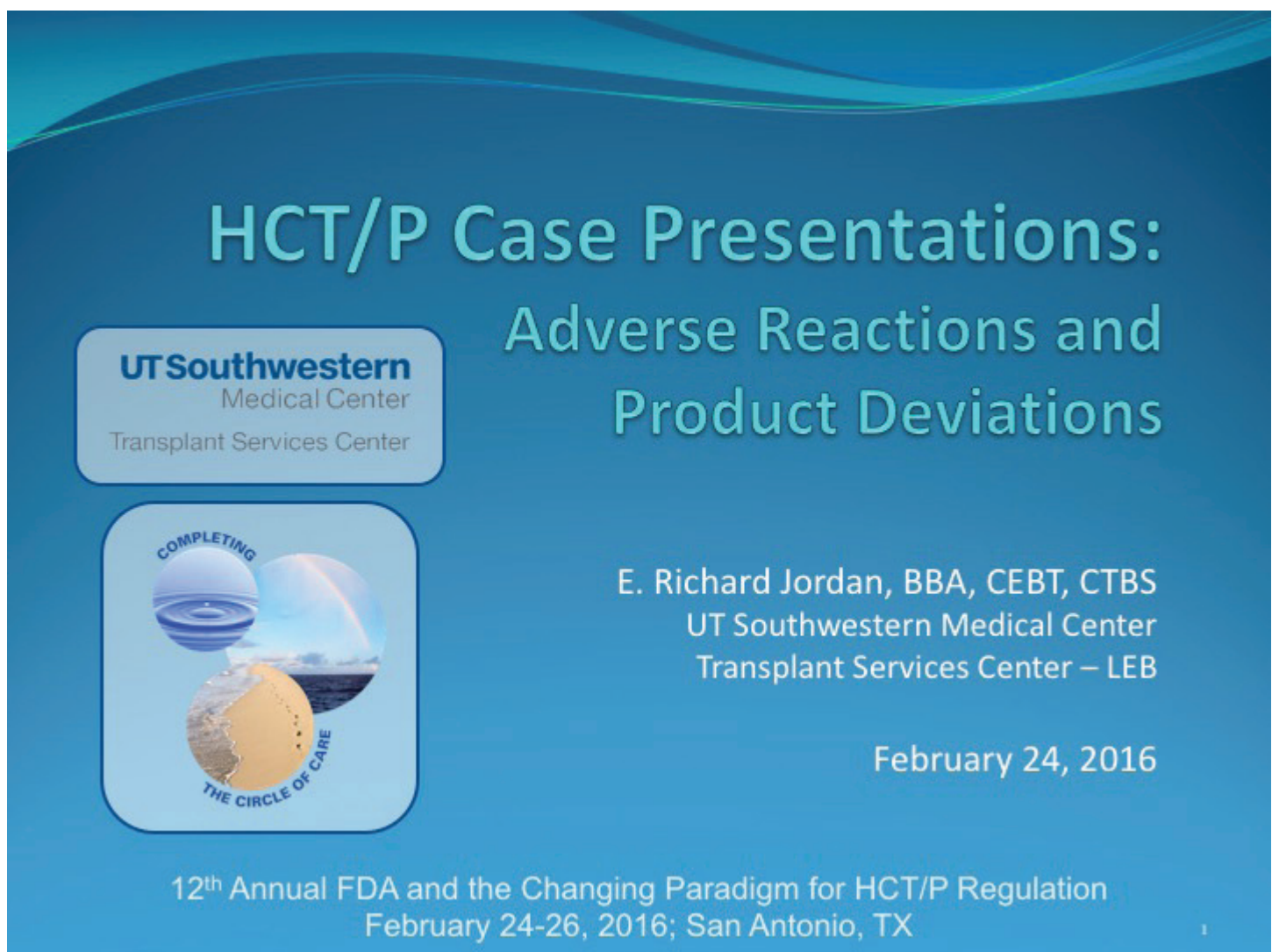


HCT/P Case Presentations: Adverse Reactions and Product Deviations

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Introduction:

Reporting adverse reactions and biologic product deviations on occasion can be confusing to those who may, fortunately, not have to do such reporting frequently. The following case studies are presented to assist in the review of situations where such reporting may be required by the Food and Drug Administration to fulfill one or more of its regulations. These requirements can be found in 21 CFR part 1271.350



HCT/P Case Presentations:
Adverse Reactions and Product Deviations

UT Southwestern
Medical Center
Transplant Services Center

COMPLETING
THE CIRCLE OF CARE

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Slide 2:

Case 1 (1 of 2)

Corneas were transplanted from a donor who was determined to be eligible based on available information (afebrile, without leukocytosis, no signs/symptoms of sepsis).

At the time of Donor Eligibility determination, blood cultures performed by the hospital prior to death were 'No Growth' at 48 hours.

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Slide 5:

Case 1a (Discussion)

What if one cornea recipient has developed endophthalmitis that may be attributable to the positive blood culture?

- HCT/P Deviation Report not required because there's no indication of sepsis.
- Medical intervention was required to treat the infections.
- Adverse Reaction Report Required - 21 CFR 1271.350 (Submit MedWatch Form 3500A to FDA within 15 days of initial receipt of information) 21 CFR 1271.350(a)(2-3)

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Slide 3:

Case 1 (2 of 2)

Several days after transplant the eye bank received final blood culture results from the organ procurement organization – positive for Fusobacterium.

What do you do?

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Slide 6:

Case 2 (1 of 1)

A cornea recipient develops symptoms 3 months post-transplant and tests positive for HCV. In the course of the investigation, the eye bank discovers that donor testing for HCV was not performed correctly.

What do you do?

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Slide 4:

Case 1 (Discussion)

- Cornea surgeons notified - Cornea recipients are without related complications.
- HCT/P Deviation Report not required because although blood cultures were positive, there's no indication of sepsis.
- No Adverse Reaction – no Adverse Reaction Report required.

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Slide 7:

Case 2 (Discussion)

- Investigate adverse reactions involving a communicable disease related to an HCT/P that were made available for distribution - 21 CFR 1271.350(a)(1)
- Notify other consignees and organizations thought to be involved in the donation.
- Adverse Reaction Report is required - 21 CFR 1271.350 (Submit MedWatch Form 3500A to FDA within 15 days of initial receipt of information)
- HCT/P Deviation Report is required because there is a violation of 21 CFR 1271.80(c) [testing]

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Slide 8:

Case 3 (1 of 2)

Donor: 19 y/o female with hanging as a cause of death. Pronounced in ER after resuscitation efforts were unsuccessful.

Corneas, musculoskeletal, and cardiovascular tissue were recovered.

Based on available information, donor was determined to be eligible and both corneas were released for transplant.

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Slide 10:

Case 3 (Discussion)

- Cornea surgeons notified - Cornea recipients are without related complications.
- HCT/P Deviation report is not required because lymphocytic myocarditis is not a communicable disease.
- No Adverse Reaction – no Adverse Reaction Report required.

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Notification of cornea surgeons is an organizational decision in this case. Notification decision should be based on Medical Director opinion and other organizational considerations such as relative risk to recipients, perceived risk to organizational reputation and public trust, etc.

Slide 9:

Case 3 (2 of 2)

Several days later the cardiac pathology report from the heart valve processor was received - indicating the donor may have had lymphocytic myocarditis at the time of death (identified on microscopic exam).

What do you do?

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Slide 11:

Case 4 (1 of 1)

An eye bank receives a post-transplant report from a cornea surgeon that the recipient has developed a *Candida glabrata* infection.

In the course of investigating the report, the eye bank finds that the recipient of the mate cornea also has an infection with the same infectious agent

What do you do?

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Slide 12:

Case 4 (Discussion)

- Investigate adverse reactions involving a communicable disease related to an HCT/P that they made available for distribution - 21 CFR 1271.350(a)(1)
- Medical intervention was required to treat the infections.
- Adverse Reaction Report Required - 21 CFR 1271.350 (Submit MedWatch Form 3500A to FDA within 15 days of initial receipt of information) 21 CFR 1271.350(a)(2-3)
- If investigation does not reveal a deviation, HCT/P Deviation Report not required.

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Slide 13:

Case 5 (1 of 2)

Donor: 69 y/o male with a history of atherosclerotic cardiovascular disease (ASCVD) which was also the cause of death. Pronounced in the emergency room after resuscitative efforts were unsuccessful. Donor Risk Assessment Interview with next of kin was unremarkable beyond ASCVD.

Corneas were recovered by the eye bank. Skin and musculoskeletal tissue were recovered by the tissue bank. Based on available information, the donor was determined to be eligible and corneas were released for transplant.

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Slide 14:

Case 5 (2 of 2)

Approximately 1 month later the Tissue Bank reported to the Eye Bank that they had received information from the donor's primary care physician that she was treating the donor for Alzheimer's.

What do you do?

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Slide 15:

Case 5 (Discussion)

- Tissue Bank shares information with eye bank.
- Cornea surgeons notified - Cornea recipients are without related complications.
- The remaining donor tissue discarded.
- Report as an HCT/P Deviation because there is a violation of 1271.50(b)(1)(i). [donor eligibility determination]
- No Adverse Reaction – no Adverse Reaction Report required.

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Donor eligibility determination failed to identify the history of Alzheimer's. The donor was not free from risk factors for, and clinical evidence of, infection due to relevant communicable disease agents and diseases.

Slide 16:

Case 6 (1 of 2)

Corneas, skin, and musculoskeletal tissue were recovered from 23 y/o female found 11:45 unresponsive after attending a party the night before where she was described as "very intoxicated". She was LKA at 09:30 when a friend heard her snoring loudly. She was transported to the ER and pronounced in the ER. No rhythm was ever obtained.

History provided by mother consisted of use of a prescription to help her sleep, social drinker, smoked pot, and smoked cigarettes. History was otherwise unremarkable.

Corneas were released for transplant. Other tissues remained in quarantine pending processing and final autopsy report.

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Slide 17:

Case 6 (2 of 2)

The final autopsy report was received several months later. COD was listed as combined toxic effects of ethanol, cocaine, heroin, and alprazolam.

Review of the donor record confirmed that there were no findings of fresh punctures or track marks found by either the recovery team nor the Medical Examiner. There was no known history that would suggest use of IV or other injection drugs.

What do you do?

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Slide 19:

Case 7 (1 of 2)

Donor: 46 y/o female with Pulmonary Embolism as the cause of death.

Corneas, skin, musculoskeletal, and cardiovascular tissue were recovered.

Based on available information corneas were released for transplant.

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Slide 18:

Case 6 (Discussion)

- Cornea surgeons notified - Cornea recipients are without related complications.
- Report as an HCT/P Deviation because there is a violation of 1271.50(b)(1)(i). [donor eligibility determination]
- No Adverse Reaction – no Adverse Reaction Report required.

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Slide 20:

Case 7 (2 of 2)

An audit of the Donor Risk Assessment Interview revealed that one question was not asked but had been marked as “No”. The question was regarding whether the donor ‘...had or had been treated for any sexually transmitted diseases in the past twelve months...’.

The next of kin was immediately re-contacted and asked the question – the answer was ‘No’.

What do you do?

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Although there is no indication of IV drug use, since we don't know how the heroine was administered, this would be reportable under the donor eligibility code, DE0201. It would be considered an unexpected event (subsequent information determined donor was ineligible).

Slide 21:

Case 7 (Discussion)

- Consignees not notified of the deviation since the correct answer did not change the donor eligibility determination.
- Report as an HCT/P Deviation because there is a violation of 1271.50(b)(1)(i). [donor eligibility determination]
- No Adverse Reaction – no Adverse Reaction Report required.

Donor eligibility determination was improperly performed and failed to determine that the donor was free from risk factors for, and clinical evidence of, infection due to relevant communicable disease agents and diseases. In this case, although there was a deviation, there were no risk factors for relevant communicable disease agents.

Slide 22:

Case 7a (Discussion)

Suppose the answer had been 'Yes' the donor had been treated for syphilis in the past twelve months?

- Notify consignees.
- Report as an HCT/P Deviation because there is a violation of 1271.50(b)(1)(i). [donor eligibility determination]
- No Adverse Reaction – no Adverse Reaction Report required.

Consignee notification is required because there were risk factors for relevant communicable disease agents.

Slide 23:

Case 8 (1 of 2)

Corneas, skin and musculoskeletal tissue were recovered from a donor who is also an organ donor. Infectious disease testing results from the organ procurement organization (OPO) are shared between all recovery organizations and used as the tests of record.

Corneas, skin and several bone grafts are released and distributed.

Slide 24:

Case 8 (2 of 2)

An audit of the testing laboratory contracted by the OPO reveals that testing for Relevant Communicable Disease Agents and Diseases are being performed in triplicate (not according to manufacturer's package insert (MPI)) and individual test results were not obtained by HCT/P establishments prior to determining donor eligibility.

What do you do?

Slide 25:

Case 8 (Discussion)

- Obtain and review triplicate test results (they're all found to be non-reactive).
- Notify consignees?
- HCT/P Deviation report required - violation of 21 CFR 1271.80(c) [testing] – Manufacturer Package Insert instructions were not followed.
- If results were positive?
- Notify Consignees.
- No Adverse Reaction – no Adverse Reaction Report required.

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This scenario is more complex than it may initially appear as the slightest variation(s) in the facts of similar scenarios could render completely different reporting requirements. Work closely with FDA staff in determining appropriate reporting. However, be aware that decisions are ultimately the responsibility of the HCT/P establishment.

Conclusion:

These eight cases studies indicate a range of potential actions which may be required as scenarios vary. In all cases it is the reportable deviation which may result in harm to the recipient or the actual occurrence of an adverse reaction that are of most concern to the FDA and of course to the eye bank and the eye banks medical director who should be involved in the review of all such incidences.